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(21) International Application Number: PCT/NL96/00478 (22) International Filing Date: 5 December 1996 (05.12.96) (30) Priority Data: 1001977 22 December 1995 (22.12.95) NL (71) Applicant (for all designated States except US): DSM N.V. [NL/NL]; Het Overloon 1, NL-6411 TE Heerlen (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): DE BRABANDER-VAN DEN BERG, Ellen, Marleen, Monique [NL/NL]; Provinciale weg Zuid 30, NL-6438 BE Schinnen (NL). BRACKMAN, Josephine, Charlotte [NL/NL]; Kerkstraat 20, NL-6174 RE Schinnen (NL). DE MAN, Hendrikus, Cornelis, Johannes [NL/NL]; Irenelaan 22, NL-6165 CP Geleen (NL). MURE-MAK, Hendrika, Anette, Petronella [NL/NL]; Ambyerstraat Noord 147, NL-6225 ED Maastricht (NL). (74) Agent: JACOBS, Monique, Sophie, Nicole; Octrooibureau DSM, P.O. Box 9, NL-6160 MA Geleen (NL).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PROCESS FOR THE PREPARATION OF A MACROMOLECULE (57) Abstract <p>The present invention relates to a process for the preparation of a macromolecule wherein a core molecule contains at least one functional group. The core molecule is alternately subjected to an addition reaction in the presence of at least a vinyl compound, and a hydrogenation reaction in a reaction mixture containing at least hydrogen and a catalyst under substantially anhydrous conditions. According to this invention, the amount of metal impurities originating from the catalyst is strongly reduced and the hydrogenation reaction is much more effective. In addition, by selection of appropriate reactants and process conditions, the amount of branching in the macromolecule is controlled.</p>		

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PROCESS FOR THE PREPARATION OF A MACROMOLECULE

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BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a process for
10 the preparation of a macromolecule, wherein a core
molecule containing at least one functional group, is
alternately subjected to an addition reaction in the
presence of a vinyl compound, and a hydrogenation reaction
in the presence of hydrogen and a catalyst under
15 substantially anhydrous conditions.

2. Description of the Related Art

Several potential applications for dendritic
macromolecules have been proposed. For instance, in Angew.
20 Chem. Int. Ed. Engl. 29 (1990), pp. 138-175, dendritic
macromolecules have been mentioned as having utility in
connection with the calibration of sieves, as catalyst
carriers, as selective membranes, and in connection with
electronic purposes and coatings. It has also been
25 proposed to employ dendritic macromolecules as impact
modifiers and cross-linking agents in various plastics.

A process relating to the preparation of a
dendritic macromolecule by alternately conducting addition
and hydrogenation reactions is disclosed in WO-A-95 02008,
30 according to which the solvent used in the hydrogenation
reaction is an alcohol which contains an amount of
ammonia. The selection of this solvent assists in the
realization of a high production capacity.

The drawback of the process described in WO-A-
35 95 02008 is that the macromolecule obtained as the end
product contains a substantial amount of undesirable
impurities in the form of metals, such as cobalt, nickel

and aluminum, which often originate from catalysts. The presence of these impurities can have deleterious effects on the color and thermal stability of the macromolecule. Consequently, in order to be suitable for certain applications, the resulting macromolecule end product must be subjected to one or more additional purification steps in order to remove at least a portion of the metal impurities present in the macromolecule. Such purification steps can be time consuming and significantly increase processing costs.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to solve the aforementioned problems associated with the related art as well as other problems by providing a process for the preparation of a macromolecule, wherein a core molecule containing at least one functional group is alternately subjected to an addition reaction in the presence of a vinyl compound and a hydrogenation reaction in the presence of hydrogen and a catalyst under substantially anhydrous conditions, in which a high capacity and selectivity in the hydrogenation is achieved and in which macromolecules with a low content of inorganic impurities are obtained.

These and other objects are achieved according to an embodiment of the present invention which involves alternately subjecting the macromolecule to an addition reaction and a hydrogenation reaction, in which the hydrogenation reaction is conducted under substantially anhydrous conditions, such that the amount of water present in the reaction mixture is less than about 4 wt.%.
25
30

By conducting the hydrogenation reaction under substantially anhydrous conditions, the macromolecules prepared according to the present invention contain a

smaller amount of metal impurities, and, consequently, exhibit improved color. Further, by practicing the process according to the present invention, macromolecules can be obtained which are colorless to light yellow and have a color better than about 20 degrees Hazen.

By contrast, other industrial processes, such as those disclosed in WO-A-93 14147 and WO-A-95 02008, are structured towards their reported objectives of optimizing process cycles, and, therefore, did not recognize the importance of anhydrous hydrogenation or the adverse affect of water on the metal impurity content of the resulting macromolecule.

In addition, in the process according to the present invention the hydrogenation reaction proceeds faster, so that possible side reactions, such as retro Michael reactions, occur at a lower rate during the hydrogenation reaction, thereby improving the control over the formation of the macromolecules.

These and other objects, features, and advantages of the present invention will become apparent from the following detailed description of preferred embodiments which illustrates, by way of example, the principles of the present invention.

25 DESCRIPTION OF THE PREFERRED EMBODIMENTS

According to an embodiment of the present invention, a process is provided for the preparation of a macromolecule from a core molecule containing at least one functional group. The process involves subjecting the core molecule to an addition reaction in the presence of a vinyl compound to form an addition reaction intermediate product. The addition reaction intermediate product is then reduced by being subjected to a hydrogenation reaction in the presence of hydrogen and a catalyst to

form an intermediate hydrogenated product. The addition and hydrogenation reactions are alternately repeated such that the addition reaction and the hydrogenation reaction are performed at least once. According to this process,

5 the hydrogenation reaction is conducted under substantially anhydrous conditions, such that the amount of water present in the reaction mixture during the hydrogenation reaction is less than about 4 wt.%.

According to another embodiment, the addition
10 reaction intermediate product and/or the intermediate hydrogenated product is/are isolated after the addition reaction and/or the hydrogenation reaction, respectively. On the other hand, according to still another alternative embodiment, the addition reaction intermediate product or
15 the intermediate hydrogenated product are not isolated until the macromolecule product is obtained.

The selectivities of the addition reaction and the hydrogenation reaction each independently are preferably higher than about 80%, more preferably higher
20 than about 95%, and most preferably higher than about 99%.

The process according to the present invention is particularly suitable, for instance, to prepare virtually completely branched macromolecules, dendrimers, such as those described for instance in WO-A-93 14147, the
25 complete disclosure of which is incorporated herein by reference. A dendrimer of a certain generation is obtained by alternately carrying out the addition reaction and the hydrogenation reaction a number of times, each time isolating the resulting reaction product. In this process
30 it is usually not necessary to purify the product obtained from each of the separate intermediate steps; generally, the product obtained in the separate intermediate steps is isolated in the sense that the excess of reagents and preferably the solvent are removed.

The number of the generation of the macromolecule equals the number of addition reactions alternately conducted. For example, after one addition reaction a molecule of the first generation is obtained.

5 After alternately carrying out three addition reactions and two hydrogenation reactions on a core molecule, a macromolecule of the third generation, that is, a macromolecule with three shells, is obtained. It is also possible to stop the preparation process after a

10 hydrogenation reaction. In that case, generations equal to 1.5, 2.5, 3.5 and higher are obtained. For example, after one addition reaction followed by one hydrogenation reaction a molecule of generation 1.5 is obtained. After alternately carrying out three addition reactions and

15 three hydrogenation reactions on a core molecule, a macromolecule of generation 3.5 is obtained.

The process according to the present invention also permits for the control of the molecular architecture -- i.e., the degree of branching -- in the resulting

20 macromolecules. Specifically, the degree of branching, and in particular the extension or further branching of existing branches of the macromolecule, is controlled by selection of the appropriate amounts of the vinyl compound and reaction conditions. For example, after alternately

25 carrying out four addition reactions and three hydrogenation reactions, a macromolecule of the fourth generation with four shells is obtained. For each shell, a different degree of branching can be obtained. For instance, the fourth generation macromolecule can be

30 prepared having 100% branching for the first shell, which means that substantially all reactive sites of the core molecule have reacted to form the first layer of branches, 0% branching for the second shell, in which only extension of the existing branches in the first shell occurs, 50%

branching in the third shell, meaning a 50% increase in the number of branches from that of the second shell, and 100% branching in the fourth shell. Thus both the size of the cavities between the branches and the generation at which the macromolecule is sterically crowded (or "sterically tight") can be influenced.

From a standpoint of reducing the loss of product due to handling, which is particularly attractive in a commercial environment, it is preferable to practice an embodiment of the process according to the present invention in which there is no intermediate isolation of the macromolecule obtained as an intermediate product after an addition or a hydrogenation reaction. This embodiment is particularly suitable where complete branching of each shell of the macromolecule is not sought.

The hydrogenation reaction is carried out in the presence of hydrogen and a catalyst. During the hydrogenation reaction less than about 4 wt.%, preferably less than about 2 wt.%, and most preferably less than 1 wt.% water is present in the reaction mixture. In order to obtain such a low water concentration in the reaction mixture, preferably, the reactants are dried before being added to the reaction mixture. Also, the hydrogenation is preferably carried out in the absence of compounds containing at least one hydroxy group, such as alcohols, and in particular low-molecular weight alcohols having 1-10 carbon atoms. Examples of such low-molecular weight alcohols are methanol, ethanol, propanol and butanol. The reaction mixture during the hydrogenation reaction would therefore contain less than about 4 wt.%, preferably less than about 2 wt.%, and most preferably less than about 1 wt.% of compounds containing at least one hydroxy group.

Suitable core molecules include, by way of

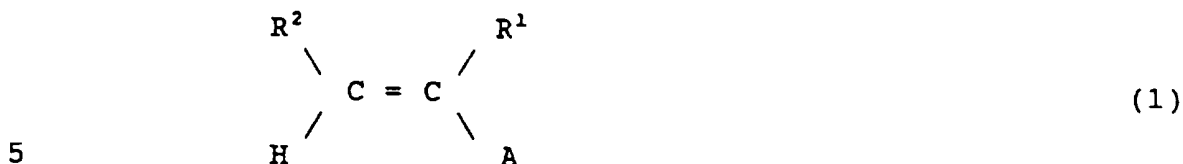
example, monomers, polymers or dendrimers which contain at least one functional group, as described in WO-A-93 14147 and WO-A-95 02008; the complete disclosure of the latter is incorporated herein by reference.

5 As referred to in the present invention, a functional group is understood to be a group which, optionally in the presence of a suitable catalyst, can react with a vinyl compound. Such functional groups include, for instance, the following: an amino group, in
10 particular a primary or secondary amino group; a hydroxyl group; a thiol group; a hydrocarbon group provided with one or more electron-withdrawing substituents, for instance a nitro group; an ester group; an amide group; a
15 ketone group; an aldehyde group; and a carboxyl group or the corresponding salt of a carboxyl group. The functional group in the core molecule preferably is a hydroxyl group, a primary amino group, and/or a secondary amino group.

 The core molecule is preferably selected from the group comprising NH_3 , polymethylene diamines,
20 dipolymethylene triamines and higher amines, glycols, and tris(1,3,5-aminomethyl)benzene. In particular, 1,4-diaminobutane is an exemplary core molecule.

 In the addition reaction, in particular a Michael condensation, the core molecule or an intermediary
25 obtained after a hydrogenation reaction is contacted with a vinyl compound, such as described for instance in WO-A-93 14147 and WO-A-95 02008.

 Suitable vinyl compounds include, by way of example, vinyl compounds comprising an electron-
30 withdrawing group which is conjugated with a double bond. In particular, the vinyl compounds can have the following formula (1):



wherein:

- 10 A = $\begin{array}{c} O \quad H \\ || \quad | \\ -C-N-R^3 \end{array}$; $\begin{array}{c} O \\ || \\ -C-O-R^3 \end{array}$; $\begin{array}{c} O \\ || \\ -C-R \end{array}$ or $-NO_2$
 R¹ = -H or $-CH_3$
 R² = -H or $-CH_3$ or a hydrocarbon compound having 2-18
 carbon atoms and containing at least one double
 bond conjugated with the double bond of formula
 15 (1) such as for example $-CH=CH_2$, $-CH=C-CH=CH_2$.
 R³ = a hydrocarbon residue having 1-18 carbon atoms
 and 1-5 cyanide groups or nitro groups.

20 Particularly suitable vinyl compounds are, for
 instance, vinyl cyanide compounds, and in particular
 acrylonitrile and methacrylonitrile (MACN). Reaction of
 the core molecule or intermediate hydrogenated molecule
 with acrylonitrile compounds provides a macromolecule with
 terminal nitril groups, which subsequently may be reduced
 25 to an amine group by the hydrogenation reaction.

 As mentioned above, the degree of branching and
 the extent of the addition reaction can be controlled by
 selection of appropriate amounts of the vinyl compound and
 reaction conditions. In practice, if it is desired to
 30 react a vinyl compound at each reactive site of the core
 or of an intermediate hydrogenation product in the
 addition reaction, the molar ratio between the number of
 vinyl compounds and the number of available reactive sites
 will preferably be higher than about 1. The ratio between
 35 the number of vinyl compounds to the number of reactive
 sites is preferably between about 1 and about 5, and more

preferably between about 1 and about 2.5. The term "reactive site" in this context refers to the sites in the core molecule or the intermediate product where an addition reaction can take place; for example, an amino
5 group (-NH_2) has two reactive sites.

On the other hand, if a lower degree of branching (that is, the degree of branching resulting from an addition reaction in which a vinyl compound is to be reacted not on each reactive site of the core molecule or
10 of an intermediate hydrogenation product) is desired, a proportionately lower vinyl compounds to reactive sites ratio is employed. Determination of the ratio required to achieve a certain amount of branching is within the skill level and understanding of a person skilled in the art,
15 and would not require an undue amount of experimentation or calculation.

If it is an objective to achieve a macromolecule or a generation of a macromolecule having extensions of the existing branches and no branching, so that for
20 instance out of two reactive sites in the NH_2 group only one reacts, the vinyl compounds to reactive sites ratio will be about 1 : 2, and preferably between 1 : 1.9 and 1 : 2.1. Another manner for achieving extension instead of branching is to use vinyl compounds which provide only one
25 reactive site upon hydrogenation.

It has been found that macromolecules can be prepared with controlled variation of the degree of branching per generation, so that the degree of branching per generation is between 0 and 100%. As referred to
30 herein, the degree of branching is understood as the ratio of tertiary amino groups to the sum of secondary amino and tertiary amino groups in a specific shell. The present invention also pertains to macromolecules per se which shells are not fully branched, or completely non-branched,

and to macromolecules that have degrees of branching which are different in each shell. In particular, the present invention pertains to a macromolecule which comprises a core molecule and at least one branch which sprouts from the core molecule, the branch consisting of amino units and extending over two or more shells, the degree of branching per shell in the macromolecule being between about 5% and about 95%. Also, the present invention pertains to a macromolecule which comprises a core molecule and at least one branch which sprouts from the core molecule, the branch consisting of amino-units and extending over two or more shells, the degree of branching per shell in the macromolecule being between about 0% and about 100% and the degree of branching not being the same in all shells. The macromolecules have two or more shells, and usually three or more shells. Preferably, the various shells of the macromolecules are composed of the same amino units. As referred to herein, an amino unit is understood to be that part of a branch or of an extension that has originated from the addition of one vinyl compound to the macromolecule. For example, if acrylonitril is used throughout the addition reactions, the amino units that make up the branches consist of either ethylcyanide groups ($-\text{CH}_2-\text{CH}_2-\text{C}\equiv\text{N}$) or propylamine groups, the propylamine groups being either primary propylamine groups ($-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$) in which case they are terminal amine groups, secondary ($-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}-$) or tertiary propylamine groups ($-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}<$).

Optionally, the addition reaction can be carried out in the presence of a catalyst. Acid as well as basic catalysts are suitable; preferably, an acid catalyst, in particular a solid acid catalyst, is selected. The advantage of solid catalysts is that they can be isolated from the reaction mixture in a simple way such as, for

instance, by filtration. The amount of solid acid catalyst generally is from about 0 mol% to about 5 mol% acid groups relative to the quantity of amino groups present. In addition, solid acid catalysts appear to be substantially inert during the hydrogenation reaction and may remain in the reaction mixture throughout the process. Therefore, the addition reaction preferably is carried out in the presence of a solid acid catalyst if a process is used in which the intermediate addition and/or hydrogenation product is not isolated. Optionally, an extra amount of solid acid catalyst can be added to the reaction mixture before a new addition reaction is started.

Suitable solid acid catalysts include, by way of example, natural clay minerals, acid applied on a solid carrier, metal oxides and sulphides, ion exchangers in the acid form, metal salts and mixed oxides, as described in K. Tanabe et al., Studies in Surface Science and Catalysis, Vol. 51, "New solid acids and bases, their catalytic properties", (1989) Kodansha (Tokyo), Elsevier (Amsterdam-Oxford-New York-Tokyo). An ion exchanger is preferably used in the acid form. Examples of suitable ion exchangers are styrene divinyl benzene copolymers with sulphonic acid groups such as, for instance, various types known under the name Amberlist or Amberlite, and sulphonic acids of perfluorated resins such as, for instance, various types known under the name Nafion-H®.

Optionally, a solvent can be used in the addition reaction. The solvent to be used in the addition reaction preferably is selected so that it contributes to a smooth, continuous run of the reactions and at the same time helps to suppress undesirable side reactions. These attributes are likely to be possessed by a solvent which reacts as little as possible with the functional groups of the reagents under the reaction conditions that are

applied. Such solvents can be selected, for instance, from the group comprising water, alcohols such as, for instance, methanol, ethanol, and isopropanol, ethers such as tetrahydrofuran, and any combination or mixture of these solvents. Preferably, water, methanol or a mixture of water and methanol is used as the solvent in the addition reaction.

Where isolation of the addition reaction intermediate product is desirable, the isolation can be accomplished, for instance, by first distilling off the excess nitrile and solvent, and subsequently cooling the reaction mixture and performing phase separation.

In an embodiment of the present invention wherein the addition reaction and hydrogenation reaction are carried out without intermediate isolation of the intermediate addition reaction product and/or intermediate hydrogenation product, the two reactions are preferably carried out in an aprotic solvent, in particular an aromatic hydrocarbon. Toluene and benzene are particularly suitable. The addition reaction is then preferably carried out in the presence of a catalyst. In such a case the reactants and the other components present in the addition reaction are preferably dried before they are added to the reaction mixture. The degree of branching can then in principle be set between 0 and 100%, in particular between about 5% and about 95%.

The pressure at which the addition reaction is carried out is not critical. The addition reaction is typically carried out at atmospheric pressure, but can also take place at elevated pressures.

The temperature at which the addition reaction is carried out (at atmospheric pressure) is typically selected between about 0°C and about 100°C, and in particular between about 20°C and about 80°C. If a low

degree of branching is desired, a low reaction temperature is preferably applied such as, for instance, between about 0°C and about 60°C, and preferably between about 20°C and about 60°C; on the other hand, if a high degree of

5 branching is desired, a high reaction temperature is preferably applied such as, for instance, between about 40°C and about 100°C, and preferably between about 60°C and about 80°C. If the reaction is carried out at elevated pressure, higher temperatures are possible.

10 Optionally, the resulting or intermediate macromolecule formed in the addition reaction can subsequently be subjected to a hydrogenation reaction in the presence of hydrogen and a hydrogenation catalyst, resulting in hydrogenation of at least a portion of the
15 end groups, for instance cyanide groups or nitro groups. Optionally, a solvent can be used in the hydrogenation reaction. As the solvent, both protic and aprotic solvents, which do not enter into an irreversible reaction with the other components of the reaction mixture, in
20 particular components such as the amines, can be employed. Suitable protic solvents are, for instance, ammonia, (di)amines, in particular (iso)propylamine, butylamine, ethylene diamine, and diaminobutane.

 The hydrogenation reaction can be carried out
25 with or without a solvent. The amount of solvent employed can be varied within wide limits. By preference, an aprotic solvent is employed. Suitable aprotic solvents are, for instance, aromatic and aliphatic aprotic solvents, such as aromatic and aliphatic hydrocarbons and
30 ethers. Examples of suitable aprotic, aromatic hydrocarbons are toluene, benzene, xylene, naphthalene, anisole, ethyl benzene, decalin and aromatic petroleum ethers. Examples of suitable aprotic aliphatic hydrocarbons are n-hexane, cyclohexane, heptane, pentane,

isobutane, benzine, and aliphatic petroleum ethers. Examples of suitable aromatic and aliphatic ethers are tetrahydrofuran, diethyl ether, methyl-t-butyl ether and anisole.

5 Particularly suitable aprotic solvents include aromatic solvents. Preferably an aromatic hydrocarbon, in particular toluene or benzene, is employed.

 An exemplary solvent is a combination of a protic and an aprotic solvent. For example, the
10 combination can include as the aprotic solvent an aromatic hydrocarbon, such as toluene, and as the protic solvent ammonia or an amine, preferably a low-boiling amine, such as isopropylamine. The protic to aprotic solvent ratio (by weight) is preferably between about 1:1 and about 10:1.

15 According to one embodiment, the solvent employed in the hydrogenation reaction is the same as the solvent employed in the addition reaction.

 During the hydrogenation reaction, the reaction mixture preferably contains from about 0 wt.% to about 50
20 wt.% ammonia relative to the total weight of the macromolecule. According to an embodiment in which acrylonitrile is employed for the addition reaction, the amount of ammonia in the mixture is preferably the equivalent of a molar ratio of ammonia to the number of
25 cyanide groups of between 0.8 and 50, and more preferably between 0.8 and 20. The advantage of the presence of ammonia is that it suppresses the undesirable side reactions during the hydrogenation reaction, such as for instance retro Michael reactions, the formation of
30 secondary amines, and cyclization reactions. In general, the optimum amount of ammonia increases as the number of end groups to be hydrogenated in the macromolecule increases, and as the generation of the macromolecule progresses.

The amount of hydrogen can be varied within wide limits. Generally, an excess of H_2 is used. The H_2 remaining after the hydrogenation reaction is usually removed after completion of the reaction.

5 Preferably, water is substantially or completely removed from the addition reaction intermediate product to be hydrogenated before the hydrogenation reaction is commenced. This can be done, for instance, by washing the macromolecule one or more times with an aprotic solvent,
10 by means of an azeotropic distillation, or by drying, for instance in a vacuum oven, so that the macromolecule preferably contains at most about 1 wt.% water, more preferably at most about 0.5 wt.%, and most preferably at most about 0.1 wt.% water.

15 The hydrogenation is typically carried out at a temperature of about 25°C to about 200°C, preferably about 30°C to about 150°C, and most preferably about 30°C to about 100°C.

 Suitable catalysts for the hydrogenation are
20 described for instance in WO-A-93 14147 and WO-A-95 02008. A metal from group VIII of the periodic table, as represented in the cover of the Handbook of Chemistry and Physics, 58th Edition, CRC Press, 1977-1978, including for instance nickel, cobalt, platinum, ruthenium, palladium,
25 and rhodium, can be employed alone or optionally on a suitable carrier.

 Exemplary hydrogenation catalysts are Raney nickel or Raney cobalt. These Raney catalysts and their preparation are described for instance in U.S. Patent No.
30 1,628,190. Raney catalysts are mostly stored under water and preferably made water free, or dehydrated, before use.

 The heterogeneous hydrogenation catalyst can be dehydrated, for instance, by drying it previously in an oven (if a non-pyrophoric catalyst is used), by washing

the catalyst one or more times with an aprotic solvent or by means of an azeotropic distillation. The catalyst preferably contains not more than about 7 wt.% water, more preferably not more than about 1 wt.% water, and most
5 preferably not more than 0.5 wt.% water, before use.

The heterogeneous hydrogenation catalyst also can be washed with different solvents successively. If Raney catalysts are employed, the catalyst suitably can be washed first with a polar, water miscible solvent and
10 subsequently washed one or more times with an aprotic solvent.

In general, the amount of hydrogenation catalyst required per amount of macromolecule to be hydrogenated increases with progressing generation of the macromolecule
15 and as the number of end groups to be hydrogenated in the macromolecule increases, and can vary, for instance, between about 2 wt.% and about 150 wt.% relative to the amount of macromolecule that is present, both calculated on a dry weight basis. For example, for the hydrogenation
20 of a macromolecule with four cyanide groups as end groups, in practice the amount of the hydrogenation catalyst typically can be between about 2 wt.% and about 15 wt.%, and in particular between about 2 wt.% and about 13 wt.%, relative to the amount of macromolecule that is present.
25 As a further example, in practice the amount of hydrogenation catalyst present for the hydrogenation of a macromolecule with 32 cyanide terminal groups typically can be between about 15 wt.% and about 45 wt.%, and in particular between about 15 wt.% and about 35 wt.%,
30 relative to the weight of the dendrimer.

Determination of the optimum amount of catalyst to be employed in the hydrogenation of the cyanide-terminated product is within the skill level and understanding of a person skilled in the art, and would

not require an undue amount of experimentation or calculation.

5 The hydrogenation reaction can for instance be carried out in a closed reactor under a H_2 atmosphere. The total pressure in the reactor is mainly dependent upon the amount of the hydrogen and the ammonia present, and is typically between about 1 bar and about 500 bar, depending on the temperature, preferably between about 10 bar and about 200 bar, and most preferably between about 10 bar and about 100 bar. The hydrogen pressure in the reactor is typically higher than about 1 bar, and preferably higher than about 10 bar.

15 When the hydrogenation reaction has run to completion, the hydrogenation catalyst can be removed from the reaction mixture. Removal of the hydrogenation catalyst can be accomplished by, for instance, causing the catalyst to precipitate by filtration under a H_2 atmosphere or by cooling the reactor under a H_2 atmosphere and, after draining the H_2 , purging the reactor with inert gas and filtering off the reactor contents. The dendrimers are present in dissolved form in the filtrate.

25 Another manner for removing the hydrogenation catalyst is to place a so-called "filter candle", that is, a filter made of sintered metal, in the reactor. The filtrate is removed from the reactor via the inside of the filter, while the catalyst remains behind in the reactor on the outside of the filter. The advantage of this method is that the reactor can be maintained pressurized so that several hydrogenation reactions can be carried out successively and hydrogen deficiency of the catalyst is avoided.

30 In the process according to the invention it is also possible to use regenerated hydrogenation catalysts. For example, Raney catalysts can be regenerated by

treating the spent catalyst for some hours with a caustic solution, for instance, an aqueous solution of NaOH, at a temperature between, for instance, about 50°C and about 70°C. After filtering off, the Raney catalyst is washed
5 with deionized water until the washing water has an approximately neutral pH; the catalyst is then dried again as described above.

The molecular weight of the macromolecule obtained in accordance with the process of the present
10 invention can vary within wide limits, such as, for instance, between about 300 and about 1,000,000, in particular between about 700 and about 100,000, and more in particular between about 1,500 and about 50,000. The generation of the macromolecule obtained as the end
15 product is typically between about 1 and about 10, preferably between about 2 and about 9, and more preferably between about 3 and about 8.

The macromolecule obtained can optionally be modified wholly or partially as described in WO-A-93 14147
20 and WO-A-95 02008. This can be done by wholly or partially reacting the functional end groups, optionally in the presence of a suitable catalyst, with suitable reagents. Examples of such reagents are α,β -unsaturated compounds substituted with electron-withdrawing groups, unsaturated
25 aliphatic esters and amides, polyamides, epoxides, acid halides, alkyl or aryl aldehydes, dicarboxylic acids, (fatty) acids, diols, (a)cyclic aldehydes, ketones phosphate esters as described in U.S. Patent No. 3,855,364, molecules with a chiral center, and/or amino
30 acids, and derivatives of these.

The invention will be further elucidated by means of the following non-limiting examples.

A process for the preparation of macromolecules is disclosed in the Dutch Application No. 1001977, filed

on December 22, 1995, in the Netherlands, the complete disclosure of which is incorporated herein by reference.

EXAMPLES

5

Determination of the color of dendrimers (colorimetric)

The color of dendrimers was determined by comparing the color of a dendrimer solution with a Hazen standard color. The following standard solutions were made
10 for this purpose.

Standard solution of 500 °H: 1.245 g of potassium chloroplatinate (K_2PtCl_6) and 1.000 g of cobalt chloride ($CoCl_2 \cdot 6H_2O$) were dissolved in a one liter
15 volumetric flask in 400 ml of water and 100 ml of hydrochloric acid ($\rho = 1.19$ g/ml), made up to 1 liter and mixed. (This solution is herein designated as solution A (500 mg Pt/l), corresponding to 500 °H.)

20 Standard solution of 50 °H: 25 ml of solution A was pipetted into a 250-ml volumetric flask, made up to 250 ml and mixed. (This solution is herein designated as solution B: 50 °H). Pipetting into Nessler tubes (volume 100 ml; ϕ 30 mm) of 5 - 10 - 15 - 20 and 30 ml,
25 respectively, of the 50°H standard solution and making up to the 50 ml mark and mixing provides standard solutions of 5, 10, 15, 20 and 30 °H, respectively.

For the purpose of comparison, 5.0 g of analysis
30 material were introduced into a 100-ml volumetric flask and made up with solvent (methanol as solvent for amine-terminated dendrimers and butanone as solvent for nitrile-terminated dendrimers). The solution was transferred into a Nessler tube and made up to the 50 ml mark.

The color of the sample solution was compared with the colors of the standard solutions by looking down into the Nessler tubes through the solution against a white background.

5 As a measurement of the color in °H, the value was reported that came closest to the color of one of the standards mentioned under 6.

10 In the examples below the following catalysts were used in the hydrogenation of the cyanide-terminated dendrimers: Raney nickel, type 2400 from Grace Davison, USA, composition according to manufacturer: 3-12% Al, 0.5-5% Cr, 2-4% Fe and 79-94.5% Ni which was optionally treated with NaOH, and Raney cobalt, type 2724 from Grace Davison, USA, composition according to manufacturer: 3-12%
15 Al, 0.5-5% Cr, 78-96% Co and 0.5-5% Ni.

Before starting the hydrogenation the catalyst and the cyanide-terminated dendrimer were dried as follows.

20 The cyanide-terminated dendrimer was dried by suspending it in toluene and then evaporating the toluene. This procedure was repeated until the evaporated toluene did not contain any water. The water content and the toluene content of the dendrimers dried in this way are stated in tables 1 and 2.

25 The catalyst was dried in two different manners. The water content of the catalysts after drying is at most 0.35 wt.%.

30 1. In the first method the catalyst was dried by suspending the weighed sample of the catalyst in 50 ml of tetrahydrofuran (THF). After stirring and fixation of the catalyst by means of a magnet, the THF was removed. This procedure was repeated three times. Next, the catalyst was washed with toluene

three times in the same manner.

2. In a second method the catalyst was dried azeotropically by suspending the catalyst in an amount of toluene and then evaporating the toluene with stirring. This procedure was repeated until the evaporated toluene did not contain any water.

Example I

In a 160-ml autoclave 61.5 g 4-cascade:1,4-diaminobutane[4]:propionitrile (DAB(ACN)₄) and 2.77 g of azeotropically dried Raney cobalt were successively suspended in 18.1 g of toluene. The autoclave was closed and inertized with nitrogen. When the nitrogen had been extracted the autoclave was brought under a hydrogen pressure of about 1 bar, 4.8 g of ammonia was added to the reaction mixture and then the hydrogen pressure was raised to 30-45 bar. The autoclave was heated and then successively kept at 55°C for 15 minutes, at 70°C for 33 minutes, at 87°C for 32 minutes, at 95°C for 10 minutes and at 106°C for 63 minutes, as indicated in table 1. During the heating additional hydrogen was supplied to prevent the pressure from dropping below 30 bar. Next, the total pressure was raised to 80 bar and the content was stirred vigorously. Upon completion of the hydrogenation the autoclave was cooled, hydrogen and ammonia were removed and the autoclave was opened. The reactor contents were filtered off after addition of a small amount of Celite 521 as filtration auxiliary agent. The filtrate containing the amine-terminated dendrimer was boiled down in a rotavapor.

The Co and the Al content of the hydrogenated dendrimer were determined by means of X-ray fluorescence and are shown in table 1. X-ray fluorescence showed that the isolated product contained less than 5 ppm of Co and

less than 20 ppm of Al. The product was nearly colorless: the color was better than 20 degrees Hazen.

Analysis of the isolated product by means of ^{13}C NMR spectroscopy and mass spectrometry showed that the product obtained had the following characteristics:

^{13}C NMR (50 MHz, D_2O): 53.4 ppm, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ (2x); 51.1 ppm, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ (4x); 39.5 ppm, CH_2NH_2 (4x); 28.8 ppm, $\text{CH}_2\text{CH}_2\text{NH}_2$ (4x); 23.9 ppm, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ (2x).

Example II

Example I was repeated, with 60.6 g 4-cascade:1,4-diaminobutane[4]:propionitrile and 7.47 g of azeotropically dried Raney cobalt being suspended in 26.1 g of toluene. 4.7 g of ammonia was added to the reaction mixture. The autoclave was heated and kept successively at 80°C for 29 minutes, at 88°C for 28 minutes, at 85°C for 197 minutes, and at 102°C for 185 minutes, as indicated in table 1.

From X-ray fluorescence it appeared that the isolated product contained less than 10 ppm of Co and less than 20 ppm of Al.

The isolated product was nearly colorless: its color was better than 20 degrees Hazen.

^{13}C NMR (50 MHz, D_2O): 53.6 ppm, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ (2x); 51.7 ppm, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$ (8x); 51.2 ppm, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ (8x); 39.6 ppm, CH_2NH_2 (8x); 28.9 ppm, $\text{CH}_2\text{CH}_2\text{NH}_2$ (8x); 24.1 ppm, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$ (2x); 22.3 ppm, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$ (4x).

Table 1: Hydrogenation of 4-cascade:1,4-diaminobutane[4]:propionitrile (DAB(ACN)₄)

Ex	dendri- mer water content (wt.%)	dendri- mer toluene content (wt.%)	tempe- rature (°C)	time (min.)	catalyst ----- dendrimer (wt.%)	NH ₃ ----- dendri- mer (wt.%)	dendri- mer ----- total (wt.%)	Co/Ni content (ppm)	Al content (ppm)
I	0.02	0.28	55	15	4.5	7.8	70.6	<5 Co	<20
			70	33					
			87	32					
			95	10					
			106	63					
II	0.02	0.28	80	29	12.4	7.8	61.3	<10 Co	<20
			88	28					
			85	197					
			102	185					
VI	0.06	26.7	50	15	13.5	0	62.8	< 7 Ni	< 15
			80	30					
			97	60					

Example III

Example II was repeated, with 45 g of a second-generation dendrimer 8-cascade:1,4-diaminobutane[4]:(1-azabutylidene)₄:propionitrile (DAB(PA)₄(ACN)₈) and 7.5 g of Raney nickel, dried by the first method, being suspended in 28.9 g of toluene. 18.6 g of ammonia was added to the reaction mixture. The autoclave was heated and kept at 110°C for 240 minutes as indicated in table 2.

From X-ray fluorescence it appeared that the product contained less than 6 ppm of Ni and less than 10 ppm of Al.

The isolated product was nearly colorless: its color was better than 20 degrees Hazen.

Example IV

Example III was repeated, with 45 g of 8-cascade:1,4-diaminobutane[4]:(1-azabutylidene)₄:propionitrile (DAB(PA)₄(ACN)₈) and 7.5 g of Raney cobalt, dried by the first method, being suspended in 28.9 g of toluene. 18.6 g of ammonia was added to the reaction mixture. The autoclave was heated and kept at 110°C for 240 minutes as indicated in table 2.

From X-ray fluorescence it appeared that the product contained less than 5 ppm of Co and less than 10 ppm of Al.

The isolated product was nearly colorless: its color was better than 20 degrees Hazen.

Table 2: hydrogenation of 1,4-diaminobutane[4]:(1-azabutylidene)₄:propionitrile
(DAB(PA)₄(ACN)₈)

Ex	dendri- mer water content (wt.%)	dendrimer toluene content (wt.%)	tempe- rature (°C)	time (min.)	catalyst ----- dendrimer (wt.%)	NH ₃ ----- dendri- mer (wt.%)	dendri- mer ----- total (wt.%)	Ni/Co (ppm)	Al (ppm)
III	0.01	2	110	240	12.7	7	57.2	<6 Ni	<10
IV	0.01	2	110	240	13.1	7.4	56.8	<5 Co	<10

Example V

Example IV was repeated, with 55 g of 32-cascade:1,4-diaminobutane[4]:(1-azabutylidene)₂₈:propionitrile (DAB(PA)₄(PA)₈(PA)₁₆(ACN)₃₂) and 12.1 g of Raney cobalt, dried by the first method, being suspended in 37.4 g of toluene. 19.8 g of ammonia was added to the reaction mixture. The autoclave was heated and kept successively at 81°C for 30 minutes and at 107°C for 10 minutes.

The isolated product was nearly colorless: its color was better than 20 degrees Hazen.

From X-ray fluorescence it appeared that the product contained less than 10 ppm of Co and less than 15 ppm of Al.

Example VI

Example I was repeated, with 58.3 g of DAB(ACN)₄ and 7.86 g of Raney nickel being suspended in toluene. The total quantity of toluene was 26.7 g.

Raney nickel was previously dried by method 1. The autoclave was closed, inertized with nitrogen and purged with hydrogen. The pressure in the autoclave was raised to 40 bar with H₂. Then the autoclave was heated to 50°C, with additional hydrogen being supplied to keep the pressure at 40 bar. The autoclave was heated further to 80°C, the pressure was raised to 80 bar and the temperature was raised further to 97°C. No ammonia was supplied. Full conversion was reached. The isolated product was nearly colorless: its color was better than 20 degrees Hazen.

From X-ray fluorescence it appeared that the product contained less than 7 ppm of Ni and less than 15 ppm of Al.

Comparative experiment A

Example II was repeated in the presence of 52.71 g of methanol, 22.7 g of DAB(ACN)₄ (7 wt.%)

water), 6.3 g of ammonia and 12.3 wt.% of Raney cobalt relative to the amount of $\text{DAB}(\text{ACN})_4$ present (5.6 g of Raney cobalt containing about 50 wt.% water). The autoclave was heated and kept at 65°C for 20 minutes.

5 The isolated product was analyzed by means of ^{13}C NMR-spectroscopy, which showed that the product obtained was 1,4-diaminobutane-n,n'-tetra-1-propylamine, $\text{DAB}(\text{PA})_4$. The conversion was virtually complete.

10 X-ray fluorescence showed that the isolated product contained 230 ppm of Co and 64 ppm of Al.

Comparative experiment B

15 Example IV was repeated in the presence of 46.87 g of methanol, 28.2 g of $\text{DAB}(\text{PA})_4(\text{ACN})_8$ (containing 20 wt.% water) and this time about 24.9% Raney cobalt relative to the amount of $\text{DAB}(\text{PA})_4(\text{ACN})_8$ present (11.2 g of Raney cobalt containing about 50 wt.% water). About 4.5 g of liquid ammonia was supplied
20 to the autoclave. The autoclave was heated and kept at 40°C for 200 minutes.

 The isolated product was analyzed by means of ^{13}C NMR-spectroscopy, which showed that the product obtained was $\text{DAB}(\text{PA})_8$.

25 X-ray fluorescence showed that the isolated product contained 465 ppm of Co and 15 ppm of Al.

Example VII

30 a. 10.0 g of $\text{DAB}(\text{PA})_4$ was mixed with toluene, after which the toluene was evaporated with a film evaporator. This procedure was performed twice. Next, the $\text{DAB}(\text{PA})_4$, together with 30 g of toluene, 10 g of Amberlist 15 and 13.4 g of ACN, was introduced into an autoclave and the autoclave was closed. The
35 autoclave was purged with N_2 . The temperature was raised to 80°C (reflux temperature of ACN), which was attended by a pressure increase to 2×10^5 Pa, and kept

at that level for 24 hours with stirring. Then the reaction mixture was cooled and the reactor was opened. A sample was taken. NMR showed that $\text{DAB}(\text{PA})_4(\text{ACN})_8$ with a degree of branching of 90% had been obtained.

5 b. 20 g of Raney cobalt, being the equivalent of 10 g of dry Raney cobalt, and 10 g of toluene were added to the reaction mixture obtained in part a. of the experiment. The autoclave was closed and purged three times with N_2 and three times with H_2 . Then the pressure
10 was raised to about 4 MPa with H_2 . Next, the temperature was raised to about 80-100°C. At a temperature of about 80°C the pressure was increased to 8 MPa. When no H_2 absorption was observed any more, the mixture was stirred for another hour. The reactor was
15 cooled down and when the temperature had declined to below 50°C, the reactor was depressurized. A sample was taken. NMR showed that $\text{DAB}(\text{PA})_4(\text{PA})_8$ with a degree of branching of 82% had been obtained.

20 Example VIII

Example VII was repeated, but now 18-20 g of NH_3 was added to the reaction mixture at the beginning of step b. Further, in order to remove the ammonia again, N_2 was passed through the reaction mixture after
25 the reactor had been depressurized. A sample was taken. NMR showed that $\text{DAB}(\text{PA})_4(\text{PA})_8$ with a degree of branching of 90% had been obtained.

Although the present invention has been
30 described in detail with reference to its presently preferred embodiments, it will be understood by those of ordinary skill in the art that various modifications and improvements to the present invention are believed to be apparent to one skilled in the art. All such
35 modifications and improvements are intended to be included within the scope of the appended following claims.

WHAT IS CLAIMED IS:

1. A process for the preparation of a macromolecule,
5 wherein a core molecule containing at least one functional group, is alternately subjected to an addition reaction in the presence of a vinyl compound and a hydrogenation reaction in the presence of hydrogen and a catalyst, characterized
10 in that the concentration of water in the reaction mixture is less than about 4 wt.% during the hydrogenation reaction.
2. A process according to claim 1, wherein the concentration of the water in the reaction mixture
15 is less than about 2 wt.% during the hydrogenation reaction.
3. A process according to claim 2, wherein the concentration of the water in the reaction mixture is less than about 1 wt.% during the hydrogenation
20 reaction.
4. A process according to anyone of claims 1-3, wherein the concentration of compounds containing at least one hydroxy group in the reaction mixture is less than about 4 wt.% during the hydrogenation
25 reaction.
5. A process according to anyone of claims 1-4, wherein an aprotic solvent is used in the hydrogenation reaction.
6. A process according to claim 5, wherein the
30 aprotic solvent in the hydrogenation reaction is toluene.
7. A process according to anyone of claims 5-6, wherein also a protic solvent in the hydrogenation reaction is used.
- 35 8. A process according to claim 7, wherein the protic solvent is ammonia or an amine.
9. Process according to anyone of claims 1-8, wherein

the reaction product obtained, after an addition reaction or after a hydrogenation reaction is isolated.

10. A process according to anyone of claims 1-9,
5 wherein a consecutive addition reaction and hydrogenation reaction are carried out in the presence of the same solvent and wherein the intermediate reaction product obtained after the addition reaction or after the hydrogenation
10 reaction is not isolated.
11. A process according to anyone of claims 1-10, wherein the addition reaction is carried out in the presence of a solid acid catalyst.
12. A process according to anyone of claims 1-11,
15 wherein in the addition reaction the ratio between on the one hand the molar quantity of vinyl compound, and on the other hand the number of reactive sites of the core molecule, or the hydrogenated intermediate product is between about
20 1 and about 2.5.
13. A process according to claim 12, wherein the addition reaction is conducted under a temperature between about 60°C and about 80°C.
14. A process according to anyone of claims 1-13,
25 wherein in the addition reaction a less than equivalent quantity of the vinyl compound relative to the number of reactive sites of the core molecule or the hydrogenated intermediate product is employed.
15. A process according to claim 14, wherein the ratio
30 between the vinyl compound and the reactive sites is between 1:1.9 and 1:2.1.
16. A process according to anyone of claims 14-15, wherein the addition reaction is conducted under a
35 temperature between about 20°C and about 60°C.
17. Macromolecule which comprises a core molecule and at least one branch which sprouts from the core

molecule, the branch consisting of amino units and extending over two or more shells, the degree of branching per shell in the macromolecule being between about 5% and about 95%.

- 5 18. Macromolecule which comprises a core molecule and at least one branch which sprouts from the core molecule, the branch consisting of amino units and extending over two or more shells, the degree of branching per shell in the macromolecule being
- 10 between about 0% and about 100% and the degree of branching not being the same in all shells.
19. Macromolecule according to claim 17 or 18, the macromolecule comprising three or more shells.
20. Macromolecule according to any one of claims 17-
- 15 19, characterized in that the macromolecule is composed of identical amino units.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08F8/04 C08C19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08F C08C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 02008 A (DSM N.V.) 19 January 1995 cited in the application see claims 1-16 ---	1
A	WO 93 14147 A (DSM N.V.) 22 July 1993 cited in the application see claims 1-25 ---	1
A	EP 0 405 266 A (BAYER AG) 2 January 1991 see claim 1 ---	1
A	US 4 656 230 A (YEN-SHIN SHYR) 7 April 1987 see claims 1-9 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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